

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 31/465, 9/00, 9/70	A1	(11) International Publication Number: WO 99/15171
		(43) International Publication Date: 1 April 1999 (01.04.99)

(21) International Application Number: PCT/SE98/01632	(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
(22) International Filing Date: 15 September 1998 (15.09.98)	
(30) Priority Data: 9703458-1 25 September 1997 (25.09.97) SE	
(71) Applicant (<i>for all designated States except US</i>): PHARMACIA & UPJOHN AB [SE/SE]; S-112 87 Stockholm (SE).	
(72) Inventors; and	
(75) Inventors/Applicants (<i>for US only</i>): ANDERSSON, Sven, Börje [SE/SE]; Tuvegatan 14, S-260 35 Ödåkra (SE). JONN, Stefan [SE/SE]; Ryttmästaregatan 7 B, S-254 53 Helsingborg (SE). LANDH, Tomas [SE/SE]; Trollebergsvägen 38 C, S-222 31 Lund (SE).	Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(74) Agent: HEDENSTRÖM, John; Pharmacia & Upjohn AB, P.O. Box 941, S-251 09 Helsingborg (SE).	

(54) Title: NICOTINE COMPOSITIONS AND METHODS OF FORMULATION THEREOF

(57) Abstract

Polar lipid formulations of nicotine in liquid crystals and colloidal dispersions thereof and precursors or offspring thereof which when in contact with body fluid and/or by the influence of body temperature, are transformed to a liquid crystal or a mixture of liquid crystals, which functions as a controlled release matrix for nicotine suitable in e.g. smoking cessation and/or replacement therapies. Disclosed compositions of said liquid crystals or dispersions thereof, their precursors or offspring containing nicotine and anti-irritants or a local analgesic, or any combination of these reduce local irritation of nicotine and masks its taste. Applicable routes of administration and devices includes buccal, using chewing gum in which liquid crystals, dispersions thereof, or precursor or offspring thereof are formulated, buccal adhesives, gels and patches, using mucoadhesive liquid crystal, dispersions thereof or precursor thereof, and mouth spray using dispersion of said liquid crystals, their precursors or offspring, nasal spray and gel using said liquid crystals or their dispersions, their precursors or offspring, topical, using said liquid crystal or their precursors or offspring in adhesive patches and gels.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		

NICOTINE COMPOSITIONS AND METHODS OF FORMULATION THEREOF

Field of the invention

5 This invention relates to compositions comprising nicotine and methods to prepare said compositions useful in drug therapy, preferably tobacco substitution or replacement of tobacco and smoking cessation.

Prior art

Nicotine replacement therapy as a smoking cessation strategy has been successful 10 in the past. Previous nicotine-containing compositions aimed towards the purpose of reducing nicotine craving for subjects wishing to stop their use of tobacco products include e.g., US 3,845,217 disclosing chewable compositions, US 4,579,858 disclosing high-viscous nicotine nose-drop compositions, AU 664 415 disclosing low-viscous nicotine-containing compositions suitable for nasal spray administration, US 4,920,989 and 15 4,953,572 disclosing the use of inhalation aerosol, BP 1,528,391 and BP 2,030,862 disclosing liquid aerosol formulations adapted as mouth sprays, and for transdermal delivery of nicotine and US 4,915,950 disclosing the manufacturing of devices for transdermal delivery of nicotine. Several products based on the above mentioned patents are now marketed on an international scale.

20 A well known side-effect of nicotine is related to its concentration dependent local irritation. This adverse effect is particularly noticeable when nicotine formulations are applied topically, including the transmucosal, also comprising buccal and nasal, and transdermal administration routes. The concentration of nicotine in several of the above mentioned inventions, and product designs thereof, is hence limited by adverse effects 25 caused by or related to its local irritation. There are, however, subjects which may have cravings for higher doses of nicotine than acceptable in applications of prior art administration forms. Furthermore, nicotine chewing gum formulations may cause unpleasant side-effects, besides local irritation, such as indigestion and nausea. As to the former increased transmucosal bioavailability decreases indigestion and hence local irritation 30 caused by nicotine in the oral region. Also nicotine nasal spray formulations described in the aforesaid patent application is causing severe local irritation besides sneezing and tearing of the eyes. GB 2 230 439 A describes nicotine lozenges with a shell or coating

containing an oral-acting local analgesic, preferably eugenol. Though not stated explicitly to be the cause of the so included local analgesic, the aforesaid disclosure is said to substantially ameliorate the sensation of burning in the mouth experienced with conventional nicotine lozenges. Similarly, nicotine-compositions formulated in lozenges containing 5 local analgesic have been disclosed in AU 662877 in which the latter agent is said to temporarily interfere with taste receptors which is said to reduce the desire to eat. Thus, while GB 2 230 439 A represent an advancement in the art of reducing local adverse effects caused by nicotine formulated in lozenges it still remains to decrease side-effects related to the local irritation caused by nicotine in general, including the above exemplified routes of administration and applicable formulations, inventions or products thereof.

EP 126,751 B1 discloses controlled release compositions for the delivery of biologically active materials. According to the invention described therein, a biologically active material is provided in formulations of amphiphilic substances capable of forming liquid crystalline phases when placed in contact with a liquid to be constituting any part 15 of the polar compartment of the then formed thermodynamically stable phase. The liquid crystalline phases utilised in the aforesaid invention are preferably, but not exclusively, the group of cubic and hexagonal, liquid crystalline phases. WO 95/26715 discloses bioadhesive compositions using fatty acid esters forming liquid crystals, preferably the group of cubic and hexagonal, liquid crystalline phases. US 5,371,109 discloses the use 20 of an L2-phase composed of mixtures of mono- and triglycerides and polar solvent as a controlled composition for biological active materials. The use of fatty acids in such mixtures is, however, not disclosed. US 5,531,925 discloses methods of preparing particles, or precursors thereof, of the aforementioned liquid crystalline phases or precursors thereof of reversed/inversed type II structure. WO 97/13528 also discloses liquid crystalline phases. Although in the latter nicotine is mentioned in the description, within a long 25 list of drugs, no compositions according to the examples may be formulated with nicotine.

Suitable stable nicotine containing formulations with or without local analgesics have heretofore not been disclosed. While is briefly mentioned in some of the above patent documents nowhere is disclosed how to formulate a stable liquid crystalline phases comprising nicotine. Surprisingly has now been found that the combination of nicotine and fatty acids is promoting the formation of liquid crystals of polar lipids. Therefore it

has now become possible to produce liquid crystals comprising nicotine suitable for controlled release applications.

Summary of the invention

Compositions for the therapeutic delivery of nicotine are provided. Said compositions, comprising nicotine, decrease adverse effects of nicotine, related to or caused by its local irritation, through controlled release of nicotine, by co-delivering antiirritants or local analgesic, or by any combination of these methods. The compositions are used for administration of nicotine. The compositions are, furthermore, applicable for, but not restricted to, nasal, buccal, pulmonary and transdermal routes of administration. Suitable, but not limiting, administration forms are nasal sprays, buccal sprays, chewing gums, tablets, lozenges, transdermal or buccal patches, nasal gels, transdermal or buccal gels, transdermal or buccal adhesives, or sprays or aerosols for administration to the lungs. As is clear from the below description a transdermal patch comprising the present invention may have a very high loading implicating that a useful transdermal patch may have a very small area thereby being useful for placing on less visible sites of a human body, such as behind the ear.

According to one aspect, the invention is directed to compositions comprising nicotine which as a total forms a liquid crystalline phase or a precursor thereof comprising at least one amphiphilic lipid in sufficient amounts to form said liquid crystalline phase. The dependent variables of which the formation of the liquid crystalline phase from a precursor formulation are preferably chosen from, but not restricted to, compositional changes, temperature, and pressure, or any combinations thereof as can be realised by those skilled in the art of phase diagrams involving the mentioned state variables.

Compositional changes are preferably those occurring when said formulations are put in contact with a body fluid and are preferably chosen from, but not restricted to, changes in solvent activity and ion activity including pH changes, or a combination thereof. Said changes can also be obtained by adding extraneous matter administered e.g. through flushing with aqueous solution prior to or after administration of the precursor at its site of action. Liquid crystalline phase formations induced by temperature are preferably, but not exclusively, those formed by the increase in temperature caused by contact with a body, preferably, but not exclusively, a human body, when said formulation is put in contact with any site of application on a body which causes the formulation to adopt a

higher temperature at which another phase is formed. Similar pressure induced phase transformations can be utilized in accordance with e.g. pressure-compositional phase diagrams known to or easily established by those skilled in the art.

According to another aspect of the invention it is directed to methods of preparing 5 dispersions, preferably colloidal dispersions, of one or more liquid crystalline phases, or precursors thereof, comprising nicotine and a local analgesic or a combination thereof. Said precursor is preferably chosen from, but not restricted to, another liquid crystalline, a solid phase, a solution phase, or any other phase structure, which is capable of undergoing phase transition by means of any of the above-mentioned state variables so to 10 transform to the desired liquid crystalline phases in question.

In yet another embodiment, the invention is directed to an article of compositions directed to the production of spontaneously forming dispersions of liquid crystalline phases in which said compositions nicotine, one fatty acid and one monoglyceride in proportions sufficient to form a liquid crystalline phase when put into contact with a polar solvent, preferably of, but not restricted to, aqueous nature, which upon further dilution with said polar solvent, or another polar solvent, undergoes transformation to a stable colloidal dispersion of the liquid crystalline phase or a precursor thereof. 15

According to another aspect, the invention is directed to formulation of liquid crystalline compositions or precursors thereof comprising at least one monoglyceride, at least 20 one fatty acid, and nicotine in which nicotine and said fatty acid forms an ion-pair complex. Formulation of said liquid crystalline phase in e.g., a buffered aqueous environment, such as saliva or mucosa, causes the nicotine-ion pair complex to be weakened at a certain pH causing nicotine to be released in a controlled fashion from the liquid crystalline matrix, its precursor or its offspring.

According to yet another aspect, the invention is directed to formulations containing 25 nicotine and a local analgesic formulated in solution, liquid crystalline phase or a precursor thereof, in colloidal dispersions of one or more liquid crystalline phases or precursors thereof.

The term "precursor" used herein and in the claims refers to any formulation or 30 state of formulation of the present invention which by means of changing one or several state variables in such a way that one or a multiple of the liquid crystalline phase(s) containing nicotine forms *in situ* as disclosed herein.

The term "offspring" used herein and in the claims refers to any resulting state of the present invention resulting from changes in the state variables after application of the present invention.

The term "nicotine" as used herein and in the claims encompasses nicotine base and its mono- and dicationic species, nicotine resinate (e.g. according to US 3,845,217) and nicotine complexes. Nicotine salts preferably, but not exclusively, encompass nicotine hydrochloride, nicotine dihydrochloride, nicotine sulphate, nicotine monotartrate, nicotine bitartrate, nicotine zinc chloride and nicotine salicylate. Further the term "nicotine" also encompasses nicotine metabolites and nicotine type compounds, preferably, but not exclusively, cotinine, myosmine, anabasine, anatabine, nornicotine, beta-nicotyrine, beta-nornicotyrine and nicotine-N-oxides.

The term "liquid crystalline phase" used herein and in the claims has the meaning of a thermodynamically stable state of matter which lacks short range order, thus not true crystalline, but possesses long range order, thus not liquid or amorphous.

The term "cubic liquid crystalline phase" and "cubic phase" as used herein has the meaning of an isotropic liquid crystalline phase whose long range order is characterized by one of the possible cubic space group arrangements as determined by X-ray scattering methods in combination with phase diagram studies, said methods being known to those skilled in the art.

The term "hexagonal liquid crystalline phase" or "hexagonal phase" as is used herein denotes an anisotropic liquid crystalline phase whose long range order is characterized by its X-ray scattering pattern revealing a two-dimensional lattice.

The term "L2-phase" as used herein and in the claims denotes an optical isotropic solution phase characterized by the lack of both long and short range order and is used synonymously to the term microemulsion.

The meaning of the "type" i.e., type I or type II, or synonymously reversed (inversed) or normal, respectively, crystalline phase as used herein and in the claims denotes the curvature of the apolar-polar interface as defined by the direction of the normal to the interface as towards the polar or apolar constituents, respectively, following the terminology used in the current literature in the art. The type of phase is readily distinguished by the behaviour of the phase upon increasing amount of polar constituents e.g., water dilution, upon which type I phases will be diluted and eventually transformed to

another phase e.g. normal micelles while phases of type II will swell to a certain point of water activity at which they will be in equilibrium with any further added polar constituents e.g. water.

The meaning of "adhesiveness" as used herein and in the appended claims denotes
5 the capacity of a liquid crystalline phase so formulated as it has the capacity to change its state by e.g. absorption of polar constituents from the surroundings of its site of application, causing it to further swell, or causing a phase transformation. This is readily appreciated, by those skilled in the art, to be a consequence of the phase behaviour of the formulation in question in the environment of the site of application with which it is striving
10 to approach uniformity in the sense of thermodynamics and mass transport which result in an adhesiveness through the driving force to reach close apposition caused by its thermodynamic degree of freedom followed by the establishment of non-covalent bonds to the surface or site of application.

The term "state variables" as used herein and in the claims denotes any of the alterable parameters defining the phase behaviour as expressed by Gibb's phase rule known to those skilled in the art.
15

The meaning of the term "thermodynamically stable" as used herein and in the appended claims denotes a physical composition whose stability with respect to the integrity of its structure is limited only by chemical degradation.

20 In the present application such anionic surfactants are preferred which are capable of forming ion pairs or salts so favouring the formation of liquid crystalline phases.

Description of the figures

Figure 1 shows a four component phase diagram oleic acid-nicotine (1:1 mole ratio)/monoolein/water illustrating various physical phases of oleic acid-nicotine (1:1 mole ratio)/monoolein/water mixtures which may be used for predicting embodiments of the invention. The phases indicated are: lamellar phase form 1 and 5, reversed hexagonal phase form 2, microemulsion of L₂ phase form 3, solid crystalline form 4, cubic phase form 6, and three-phase dispersion area 7. Phase determination by means of small angle X-ray and polarizing microscopy was performed according to Landh, T., J. Phys. Chem. 98, 8453 - 8467, 1994. Examples of phase progression upon the addition of aqueous solution are shown in 8 and 9.
25
30

Figure 2 shows *in vitro* over time (minutes) release of nicotine performed in USP paddle dissolution test. Compositions of samples are given in Table 1.

Figure 3 shows a buccal patch device with a release liner 1, an optional empty cavity 2, a controlled release matrix 3 of any of the liquid crystalline compositions mentioned herein and a backing 4.

Figure 4 shows *in vitro* skin (pig skin from the back) permeation over time (minutes) of nicotine from the liquid crystalline phases given in Table 2. The experiments were performed in a Franz diffusion cell with a available diffusion area of 1.8 cm². Experiments were performed at room temperature and with a receptor phase at 37 centigrades. About 180 mg of samples in Table 2 were applied to the skin. Two control solutions were employed - control sol. 1 and 2 respectively, consisting of 114 mg nicotine/g water (pH = 10.80) and 114 mg/g phosphate buffer (pH = 6.95).

Figure 5 shows examples of *in vitro* permeation of nicotine through pig buccal epithelium. Compositions of the applied liquid crystalline phases are given in Table 3. The experiments were performed in a Franz diffusion cell with a available diffusion area of 1.8 cm². Experiments were performed at room temperature and with a receptor phase at 37 centigrades. About 55 mg of samples in Table 3 were applied to the buccal epithelium corresponding to an amount of 1 mg nicotine per experiment. Experiments, conditions and average fluxes of permeated nicotine are given in Table 4.

Figure 6 shows *in vitro* release of nicotine over time (minutes) from liquid crystalline phase compositions formulated in a chewing gum base with the appropriate excipients known to those skilled in the art. Sample 1, shown with the line having a diamond symbol, corresponds to commercially available Nicorette® 2 mg as manufactured by Pharmacia & Upjohn.. Compositions of sample 2, shown with the line having a square symbol, and of sample 3, shown with the line having a triangle symbol, are given in Example 8. Experiments were essentially performed as described in US 5,087,424.

Table 1*Wt % of components*

Sample No	Glycerol-monoolein	Oleic acid	Nicotine	Water	Buffer pH 5	Buffer pH 7
S1:1	47.50	1.84	3.16	47.50		
S1:2	47.50	1.84	3.16	47.50		
S2:1	47.50	3.18	1.82	47.50		
S2:2	47.50	3.18	1.82	47.50		
S4:1	23.75	3.18	1.82	71.25		
S4:2	23.75	3.18	1.82	71.25		
S5:1	47.50	4.20	0.80	47.50		
S5:2	47.50	4.20	0.80	47.50		
S6:1	71.25	3.18	1.82	23.75		
S6:2	71.25	3.18	1.82	23.75		
S7:1	47.50	3.18	1.82		47.50	
S7:2	47.50	3.18	1.82		47.50	
S9:1	47.50	3.18	1.82			47.50
S9:2	47.50	3.18	1.82			47.50

5

Table 2*Wt % of components*

10

Sample No	Glycerol-monoolein	Oleic acid	Nicotine	Benzyl alcohol	Glycerol	Water	Buffer pH 7
1	45.96	11.50	11.47		11.56		19.51
2	45.96	20.07	11.46		11.56		10.97
3	45.95	11.50	11.46		11.55	19.54	
4	2.00	0.35	1.00	0.90		95.75	

Table 3*Amount of components in gram.*

15

Sample No	Glycerol-monoolein	Oleic acid	Nicotine	Water	Buffer pH 7
1	4.7502	0.3182	0.1818	4.7484	
4	2.3759	0.3180	0.1818	7.1259	
6	7.1253	0.3184	0.1825	2.3741	
9	4.7503	0.3182	0.1817		4.7501

Table 4

Average of fluxes of nicotine ($\mu\text{g}/\text{cm}^2/\text{h} \pm \text{SD}$) (n=3)

(Experiment 1a, 1b, 1c, 1d and 2)*

5

Sample No	Experiment 1a	Experiment 1b	Experiment 1c	Experiment 1d	Experiment 2
1	$132 \pm 68 **$	112 ± 41	165 ± 76	117 ± 55	257 ± 29
4	229 ± 75	89 ± 15	$226 \pm 0 **$	134 ± 31	201 ± 49
6	166 ± 44	82 ± 31	$223 \pm 81 **$	147 ± 41	160 ± 51
9	249 ± 89	134 ± 9	146 ± 53	143 ± 37	277 ± 101

- *): 1a: Artificial saliva as donorphase, backing membrane on cubic phases.
- 1b: Artificial saliva as donorphase, no backing membrane on cubic phases.
- 1c: Buffer pH 7 as donorphase, backing membrane on cubic phases.
- 1d: Buffer pH 7 as donorphase, no backing membrane on cubic phases.
- 2: No donorphase, backing membrane on cubic phases.

**) n=2

10

Detailed description of the invention

Compositions of the invention includes an active drug, preferably nicotine. More precisely, the compositions comprise nicotine formulated in liquid crystalline phases or any precursor or offspring thereof, and dispersions, preferably, but not restricted to, 15 colloidal dispersions of said liquid crystalline phases, their precursors or offspring. Specifically the invention includes controlled release compositions directed to formulations of the biologically active compound, preferably, but not exclusively, nicotine, in type I and II cubic liquid crystalline phases, type I and II hexagonal liquid crystalline phases, type I and II intermediate liquid crystalline phases, and lamellar phases, in all cases irrespective of space group arrangement, and precursors of or offspring to said liquid crystalline phases, including any different phase or mixture thereof as adopted upon or during application of the formulation by the so induced change or changes taking place through changes of a physical and or a chemical nature having an effect on one or more of the state variables defining the system.

20

Precursor and offspring phases thus include, besides the above mentioned liquid crystalline phases, any phase which is not characterized as a liquid crystalline phase including, but not restricted to, solid phases, solution phases of micellar type I and II, so-

lution phase of bilayered type including the sponge phase (L₃ phase), the L₂ phase, and true solutions.

Preferably compositions of the invention relates to the use of said liquid crystalline formulations, precursors thereof and offspring thereof in tobacco substitution, smoking cessation and smoking replacement. More specifically, said liquid crystalline formulations, precursors thereof and offspring thereof are useful in said therapies when applied alone, or in appropriate devices known to those skilled in the arts of drug delivery and dosage forms, transdermally and through mucosa. The aforementioned liquid crystalline formulations, precursors and offspring thereof can be applied to plasters, patches, chewing gum, lozenges or other devices used in combination or in conjunction with said liquid crystalline formulations, precursors and offspring thereof. More specifically, the aforesaid liquid crystalline formulations, precursors thereof and offspring to are preferably applied as, or in conjunction with, transdermal dosage forms of nicotine and buccal dosage forms of nicotine. Most preferably, said liquid crystalline formulations, precursors and offspring thereof are applicable to buccal delivery of nicotine in several dosage forms, including, but not restricted to, chewing gum, lozenges, sublingual tablets and patches, including dosage forms used as wet or chewable tobacco replacement. Aforementioned compositions of said liquid crystalline formulations, precursors and offspring thereof are applicable to coat a bulk carrier system of preferably, but not restricted to, inert nature. Most preferably, said coating is applied on starch granules or powder, or plastic or other polymeric material.

Formulations of the aforementioned dispersed liquid crystalline formulations, precursors and offspring thereof nicotine comprising a biologically active agent, preferably, but not exclusively, being nicotine, in which the liquid crystalline phase, its precursors or offspring are preferably selected from, but not restricted to, colloidal particles suitable for nasal spray or drop dosage forms and mouth spray or drop dosage forms. The dispersed liquid crystalline formulations, precursors and offspring thereof, are preferably selected from the group of, but not restricted to, type I and II cubic liquid crystalline phases, type I and II hexagonal liquid crystalline phases, type I and II intermediate liquid crystalline phases, and lamellar phases, in all cases irrespective of space group arrangement, and precursors of or offspring to said liquid crystalline phases, including any different phase or mixture thereof than adopted upon or during application of the formula-

tion by the so induced change or changes taking place through changes of a physical and or a chemical nature having an effect on one or more of the state variables defining the system. Stable dispersed particles of the aforementioned liquid crystalline phase or mixture of phases or their precursors or offspring are readily produced by various fragmentation methods known to those skilled in the art. Preferable is spontaneous formation of stable colloidal dispersions of the aforementioned liquid crystalline phase or mixture of phases or their precursors. The aforementioned colloidal particulate formulations, containing nicotine, of the aforesaid liquid crystalline phases or precursors or offspring thereof can be applied to nasal and buccal/sublingual drop and spray dosage forms and pulmonary aerosol dosage form or other devices used in combination or in conjunction with said liquid crystalline formulations, precursors or offspring thereof. More specifically, the aforesaid liquid crystalline formulations, precursors and offspring thereof are preferably applied in, or in conjunction with, dosage forms intended for nasal, pulmonary or buccal administration of nicotine.

15 Compositions of the invention comprise co-formulations of nicotine and preferably, but not exclusively, local topical analgesics. Said compositions include a topical local analgesic chosen from the following, non-limiting examples, bensyl alcohol, benzocaine, chlorbutanol, chloroprocaine, clove, eugenol, lidocain, lidocain hydrochloride, mepivacaine, phenol, prilocaine, procaine, tetracaine, tetracaine hydrochloride and salicyl alcohol, or combinations thereof. Preferably, said compositions are formulated in solution or in the aforesaid formulations of the aforementioned liquid crystalline phases, their precursors or offspring and colloidal dispersions thereof. Said formulations exhibit reduced side-effects related to or caused by the local irritation originating from nicotine through blocking peripheral pain receptors which otherwise would be occupied by nicotine.

20 25 Specifically, compositions of the invention include one or more surface active agents, preferably, but not restricted to, one or more polar lipids, chosen from the non-limiting group of glycolipids, phospholipids, monoglycerides and diglycerides or a mixture thereof, preferably those polar lipids which are known, to those skilled in the art, to form liquid crystalline phases in equilibrium with any of the factors defined by a state variable.

More specifically, compositions of the invention include one or more biologically active agents, preferably nicotine, one or more monoglycerides preferably chosen from,

but not restricted to, the group consisting of glycerol esters of palmitoleic acid, oleic acid, linoleic, linolenic and arachidonic acid. Most preferable is the glycerol ester of oleic acid. Optional components besides usual pharmaceutical excipients, include, but are not restricted to, one or more fatty acids preferably chosen from, but not restricted to, the 5 group of stearic acid, palmitic acid, oleic acid, linoleic acid, linolenic acid, arachidonic acid, one or more polar solutions, such as aqueous solutions, glycerol or propyleneglycol, or a mixture thereof, one or more local analgesic(s), all components in relative amounts so as the formulation forms or is capable of forming a liquid crystalline phase by change of any of the state variables composition, temperature and pressure, or a combination thereof. In addition are included usually employed pharmaceutical excipients such 10 as flavouring agents, sweeteners, buffering agents, preservatives and such components can be added without departing from the gist of the invention.

The embodiments, practice and methods of manufacturing the compositions of this invention is further illustrated by the following non-limiting examples.

15 **Example 1**

Glycerol monooleate, oleic acid, nicotine, glycerol purum and water according to the following composition

Component:	Weight %:
Glycerol monooleate	45
Oleic acid	10
Nicotine	10
Glycerol	10
Phosphate buffer (pH 7.0)	15

20 are mixed at room temperature. The above example can be prepared in different ways. One way is as follows: to solid glycerol monooleate is added oleic acid and the mixture is allowed to form a solution to which nicotine is added. To the so obtained solution glycerol is added and the mixture is allowed to form a solution to which water is added to form a cubic liquid crystalline phase.

This composition of the invention in this application is useful in tobacco substitution, replacement and cessation therapies in a number of different ways. The composition is inserted as an adhesive gel applied directly to the buccal mucosa at which site nicotine is delivered through it. The composition is melted and poured into patch devices as illustrated in Figure 3 which is applied to a desired topical site of action such as the inner cheek at which site nicotine is released.

Example 2

Compositions according to Table 1 were prepared in duplicates as described in Example 1 and the *in vitro* release of nicotine in phosphate buffer (pH 7.0) from the compositions was determined by means of commercially available instrument for testing dissolution according to USP. The results are shown in Figure 2.

It is readily appreciated that the composition controls the rate of release. Important factors are the nicotine:oleic acid ratio and the water content. It is thus shown that the present invention can be used to control the release rate of nicotine.

Example 3

Glycerol monooleate, oleic acid, bensyl alcohol, nicotine, and water were mixed according to the following composition

Component:	Weight %:
Glycerol monooleate	8
Oleic acid	4
Bensyl alcohol	4
Nicotine	4
Water	80

The above example can be prepared in different ways. One way is as follows: to solid glycerol monooleate is added oleic acid and bensyl alcohol and the mixture is allowed to form a solution to which nicotine is added. To the so obtained solution water is added and the mixture is allowed to form a hexagonal liquid crystalline phase of type I.

This composition of the invention in this application is useful in tobacco substitution, replacement and cessation therapies in a number of different ways. The composition

is inserted as an adhesive gel applied directly to the buccal mucosa at which site nicotine is delivered through it. The composition is melted and poured into patch devices as illustrated in Figure 3 which is applied to a desired topical site of action such as the inner cheek at which site nicotine is released.

5 **Example 4**

Glycerol monooleate, oleic acid, benzocaine, and nicotine were mixed in the following proportions:

Component:	Weight %:
Glycerol monooleate	2
Oleic acid	1
Benzocaine	1
Nicotine	1
Water	95

10 The above example can be prepared in different ways. One way is as follows: to solid glycerol monooleate is added oleic acid and nicotine and the mixture is allowed to form a solution to which benzocaine is added and let to dissolve. To the so obtained solution one fifth of the total amount of water as indicated in the table is added and the mixture is allowed to form a hexagonal liquid crystalline phase of type I to which the remaining
15 water is added upon which a stable colloidal dispersion is spontaneously formed. The composition of the invention of this application is applicable in tobacco substitution, replacement and cessation therapies in a number of different ways as exemplified in the following. The composition is dropable and sprayable using a standard device for nasal administration of nicotine. For similar purposes, it is useful as mouth drops or spray.
20 Furthermore, it forms liquid aerosols using standard devices known to those skilled in the art with particle sizes in the range of the size of colloidal particles suited for pulmonary delivery of nicotine through the lung mucosa.

Example 5

Bensyl alcohol and nicotine is mixed to form a solution to which water is added to reach a final composition of:

Component:	Weight %:
Nicotine	1
Bensyl alcohol	1
Water	98

5

The above example can be prepared in different ways and optional components such as preservatives, buffer, sweetness and flavouring agents can be added. The composition can be delivered to the nasal mucosa by means of a metered spray device such as described in US 4,579,858 for use in tobacco substitution, replacement and cessation therapies. Furthermore, the composition can be used similarly as a mouth spray for application of the solution directly to the oral region and its mucosal lining.

Example 6

Compositions according to Table 2 were prepared as described in Example 1 above and tested for the *in vitro* skin permeation of nicotine. The results are shown in Figure 4 and the experimental design as described in the figure legend. It is readily appreciated that the current invention can be used for controlled skin permeation of nicotine.

Example 7

Compositions according to Table 3 were prepared as described in Example 1 and tested for the *in vitro* pig buccal epithelium permeation of nicotine. The results are given in Figure 5 with average nicotine fluxes compiled in Table 4. The experimental design is given in the legend to Table 4. It is readily appreciated that the current invention provide controlled release of nicotine and controlled fluxes and permeation through pig buccal epithelium *in vitro*.

Example 8

Compositions as below

Component:	Comp. 2	Comp. 3
	Weight %	
Glycerol monooleate	45.95	45.95
Oleic acid	11.50	20.02
Nicotine	11.46	11.46
Glycerol	11.55	11.55
Buffer pH 7	19.54	11.02

can be mixed with a gum base and optional flavouring agents according to the following

5 example

Component:	Weight %:
Liquid crystalline phase composition according to comp. 2 or 3 above	2
Gum base (from Dreyco)	77
Sorbitol power	15
Sorbitol solution (70 %)	4
Flavouring agents	2

which with the appropriate techniques can be treated by conventional means to result in a chewing gum. The *in vitro* release of nicotine from the above chewing gum formulations determined according to US 5,087,424 is shown in Figure 6 together with that of Ni-
10 corette® 2 mg. It is readily appreciated by those skilled in the art that the composition controls the release rate of nicotine. Also the use of precursors to the herein disclosed liquid crystalline phases is readily appreciated in which case the change is brought out by change in state variables chosen from chemical composition, preferably of aqueous activity, or body temperature, or a combination thereof.

15 Further aspects of the invention can be appreciated from figure 1.

Figure 1 shows a triangular diagram used to illustrate the phase behaviour of a four component system consisting of oleic acid:nicotine, glycerol monooleate and water. The

non-limiting example of phase behaviour shown in figure 1 represent 1:1 molar ratio of the oleic acid:nicotine mixture. Other ratios are applicable as well.

Shown in this diagram are some of the physical phases formed at various compositions represented by the diagram. These phases may be, for example, a water-rich one-dimensional lamellar liquid crystalline phase 1, a hexagonal type II liquid crystalline phase 2, a free-flowing liquid phase 3, a solid crystalline phase 4, a water-poor one-dimensional lamellar liquid crystalline phase 5 and a three-dimensional cubic liquid crystalline phase of type II 6.

It can be appreciated from the figure that a composition of phase 3 along the indicated line 8 will upon contact with water or any polar liquid such as saliva or any other body fluid changes effectively the physical state of the formulation towards the water corner along line 8. Thus by exposure to more water the free-fluid composition will increase its viscosity once it adopts the hexagonal liquid crystalline state of type II and subsequently enter more-phase areas (not shown in figure 1) to finally enter a three component phase area in which the cubic liquid crystalline phase coexist with the lamellar phase 1 according to the composition given along line 8. Within this three-phase area the cubic liquid crystalline phase 6 is easily dispersed and form small particles surrounded by the lamellar phase 1.

As known to those skilled in the art adhesiveness to such surfaces as the mucous lining of the mouth is obtained and significantly increased through the absorption of water and the successive changes of physical states such as appreciated along line 8 in figure 1.

Similar a solid crystalline phase 4 with a composition along line 9 goes through successive changes of physical states upon the uptake or addition of water as illustrated along line 9 to finally enter the aforementioned three-phase area illustrated along line 8.

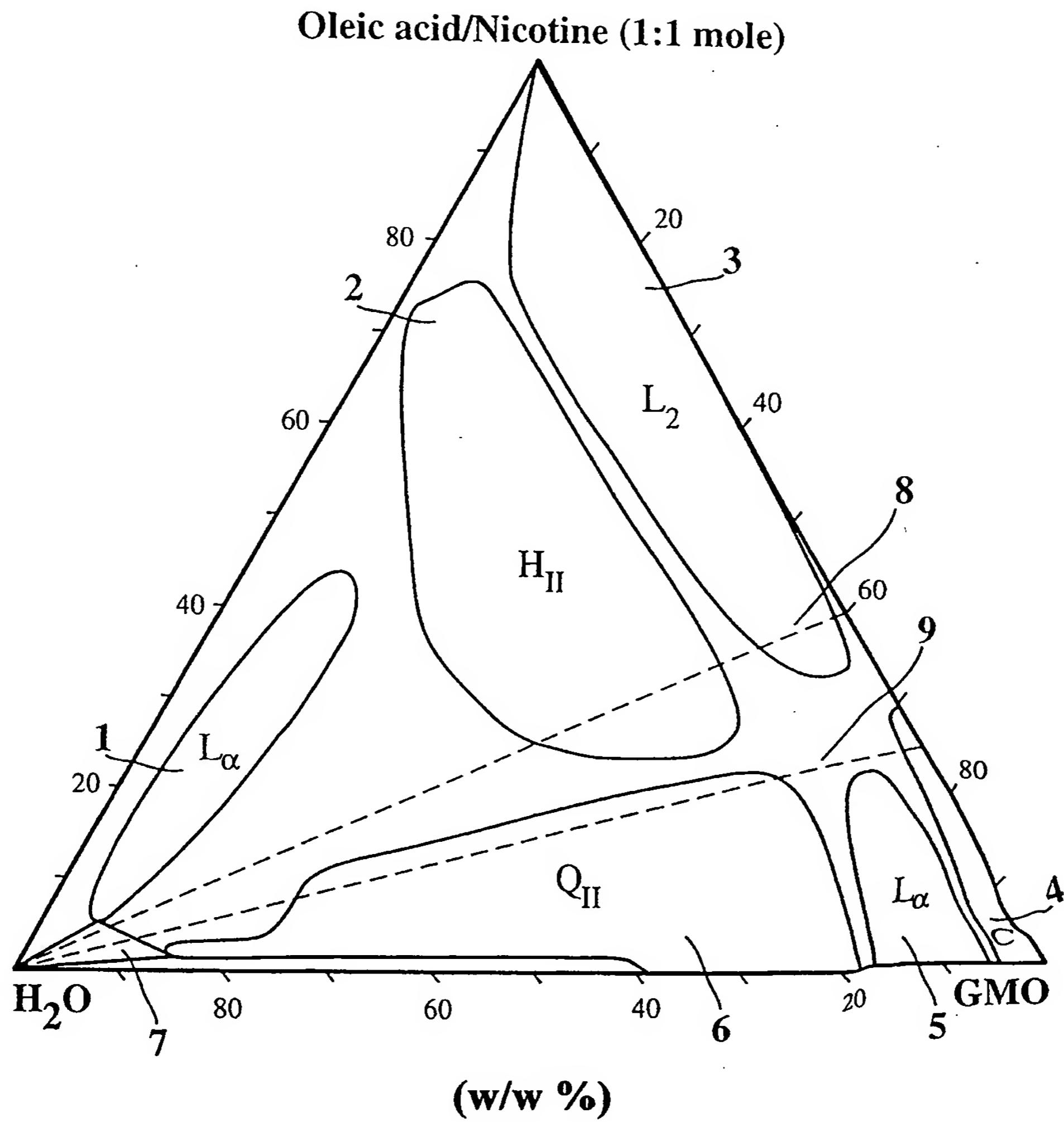
Above has been disclosed utility of nicotine-containing liquid crystalline phases for tobacco substitution or replacement of tobacco and smoking cessation. Anyhow, for persons skilled in the art use of said phases is evident for treatment of other indications, such as Alzheimer's disease, Parkinson's disease and ulcerative colitis, for which it is known that nicotine has a curative effect.

CLAIMS

1. A composition comprising nicotine and, for reducing local nicotine-related irritation, a local analgesic or a mixture of local analgesics.
2. A composition comprising nicotine, one or more polar lipids and one or more anionic surfactants in sufficient amounts to form a liquid crystalline phase or a precursor or offspring thereof when placed in a polar solvent.
 - 5 3. A composition according to claim 2 wherein the polar solvent is an aqueous solutions, glycerol or propyleneglycol, or a mixture thereof.
 4. A composition according to anyone of claims 2 or 3 wherein the liquid crystal-line phase or precursor or offspring thereof is anyone of the below types:
 - 10 type I or type II cubic liquid crystalline phases,
 - type I or type II hexagonal liquid crystalline phases,
 - type I or type II intermediate liquid crystalline phases, and lamellar phases, in all cases irrespective of space group arrangement, and precursors of or offspring to said
 - 15 liquid crystalline phases, including any different phase or mixture thereof as adopted upon or during application of the formulation by the so induced change or changes taking place through changes of a physical and or a chemical nature having an effect on one or more of the state variables defining the system,
 - solid phases,
 - 20 solution phases of micellar type I or type II,
 - solution phase of bilayered type including the sponge phase (L₃ phase), the L₂ phase, microemulsions, and true solutions.
 5. A composition according to anyone of claims 2 - 4 wherein the one or more polar lipids are monoglycerides.
 - 25 6. A composition according to anyone of claims 2 - 5 wherein the one or more anionic surfactants are fatty acids.
 7. A composition according to claim 6 wherein the one or more fatty acid(s) is/are chosen from the group consisting of stearic acid, palmitic acid, oleic acid, linoleic acid, linolenic acid and arachidonic acid.
 - 30 8. A composition according to claim 7 wherein the fatty acid is oleic acid.
 9. A composition according to claim 1 further comprising one or more mono-glycerides.

10. A composition according to anyone of claims 2 - 9 further comprising a local analgesic or a mixture of local analgesics.
11. A composition according to anyone of the preceding claims wherein the local analgesic(s) is/are selected from bensyl alcohol, benzocaine, chlorbutanol, chloroprocaine, clove, eugenol, lidocain, lidocain hydrochloride, mepivacaine, phenol, prilocaine, procaine, tetracaine, tetracaine hydrochloride and salicyl alcohol, or combinations thereof.
12. A composition according to claim 11 wherein the local analgesic is bensocaine.
13. A composition according to claim 11 wherein the local analgesic is bensyl alcohol.
14. A composition according to anyone of claims 4 - 13 wherein the one or more monoglyceride(s) is/are chosen from the group consisting of glycerol esters of palmitoleic acid, oleic acid, linoleic, linolenic and arachidonic acid.
15. A composition according to anyone of claims 4 - 13 wherein the monoglyceride is monoolein.
16. A composition according to anyone of claims 4 - 13 wherein the monoglyceride is monolinolein.
17. A composition according to anyone of the preceding claims, optionally further comprising pharmaceutically acceptable excipients, for use as a pharmaceutical.
- 20 18. A composition according to claim 17 wherein the optional pharmaceutically acceptable excipients are chosen from the group consisting of flavouring agents, sweeteners, buffering agents and preservatives.
19. A composition according to anyone of claims 17 or 18 for use in tobacco substitution, replacement of tobacco or smoking cessation.
- 25 20. A composition according to anyone of claims 17 or 18 for treating Alzheimer's disease, Parkinson's disease or ulcerative colitis.
21. A composition according to anyone of claims 17 - 20 for nasal, buccal, transdermal, mucosal or pulmonary administration.
22. A composition according to anyone of claims 17 - 20 for administration via a nasal spray or gel, a buccal spray, a chewing gum, a tablet, a lozenge, a transdermal patch, adhesive or gel, a buccal patch, adhesive or gel, or a spray or an aerosol for administration to the lungs.

23. A composition according to anyone of claims 17 - 20 for transdermal administration behind the ear of a human body.
24. Method for manufacturing a nicotine-containing composition comprising mixing nicotine and one or more polar lipids and one or more anionic surfactants in sufficient amounts to form a liquid crystalline phase or a precursor or offspring thereof when placed in a polar solvent.
 - 5
25. Method according to claim 24 wherein the one or more polar lipids are monoglycerides.
26. Method according to anyone of claims 24 or 25 wherein the one or more anionic surfactants are fatty acids.
 - 10
27. Method according to claim 26 wherein the one or more fatty acid(s) is/are chosen from the group consisting of stearic acid, palmitic acid, oleic acid, linoleic acid, linolenic acid and arachidonic acid.
28. Method according to claim 27 wherein the fatty acid is oleic acid.
 - 15
29. Method according to anyone of claims 25 - 28 wherein the monoglyceride is monoolein.
30. Method according to anyone of claims 25 - 28 wherein the monoglyceride is monolinolein.
31. Method according to anyone of claims 24 - 30 wherein with the other ingredients is mixed a local analgesic or a mixture of local analgesics.
 - 20
32. Method according to claim 31 wherein the local analgesic(s) is/are selected from bensyl alcohol, benzocaine, chlorbutanol, chlorprocaine, clove, eugenol, lidocain, lidocain hydrochloride, mepivacaine, phenol, prilocaine, procaine, tetracaine, tetracaine hydrochloride and salicyl alcohol, or combinations thereof.
33. Method according to claim 32 wherein the local analgesic is bensocaine.
 - 25
34. Method according to claim 32 wherein the local analgesic is bensyl alcohol.
35. Method of achieving cessation of using tobacco or of obtaining replacement of using tobacco whereby a composition according to anyone of claims 1 - 23 is administered to a human being in need thereof.
36. Method for treating Alzheimer's disease, Parkinson's disease or ulcerative colitis whereby a composition according to anyone of claims 1 - 23 is administered to a human being in need thereof.
 - 30

1/6**Fig. 1**

2/6

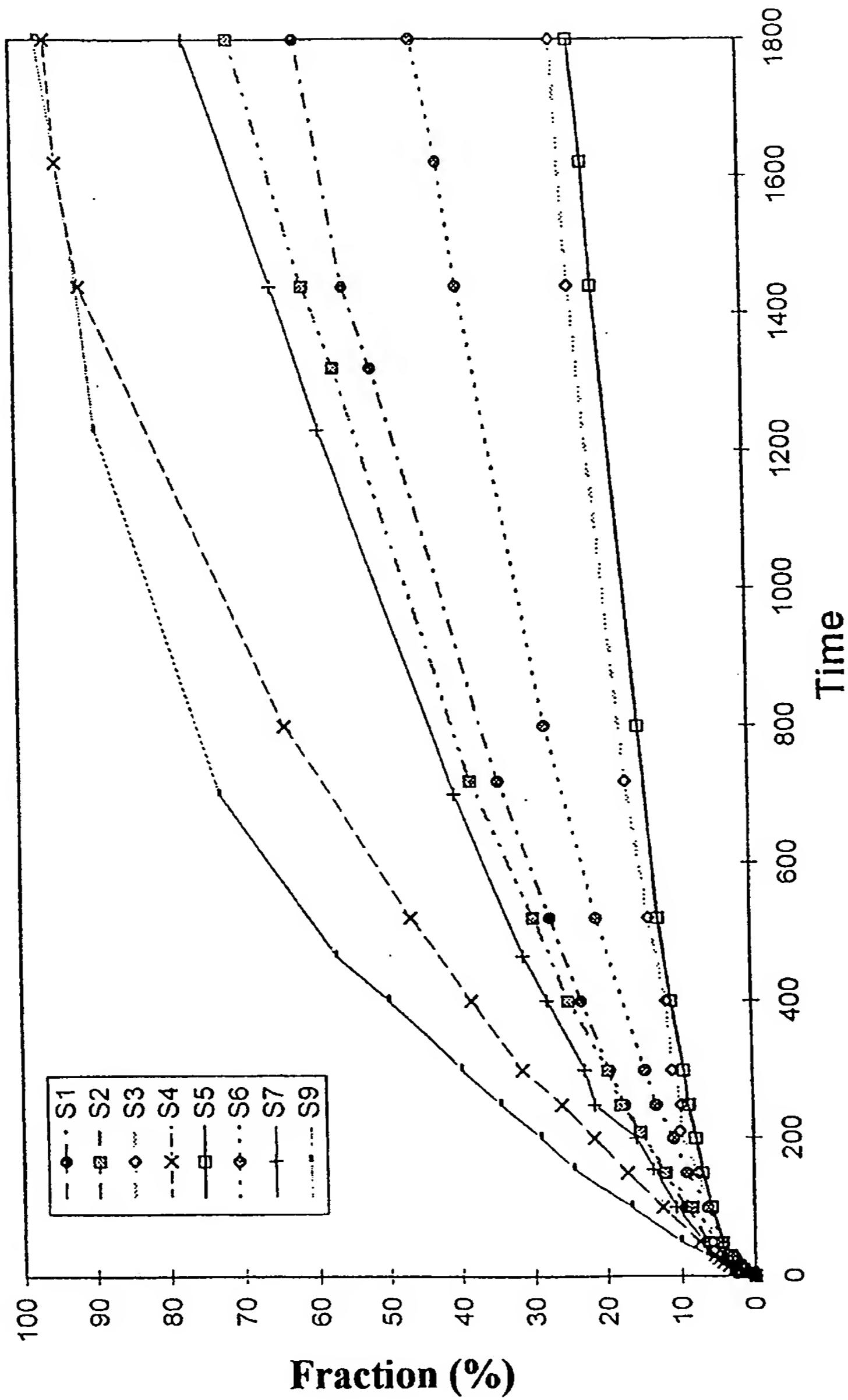


Fig. 2

3/6

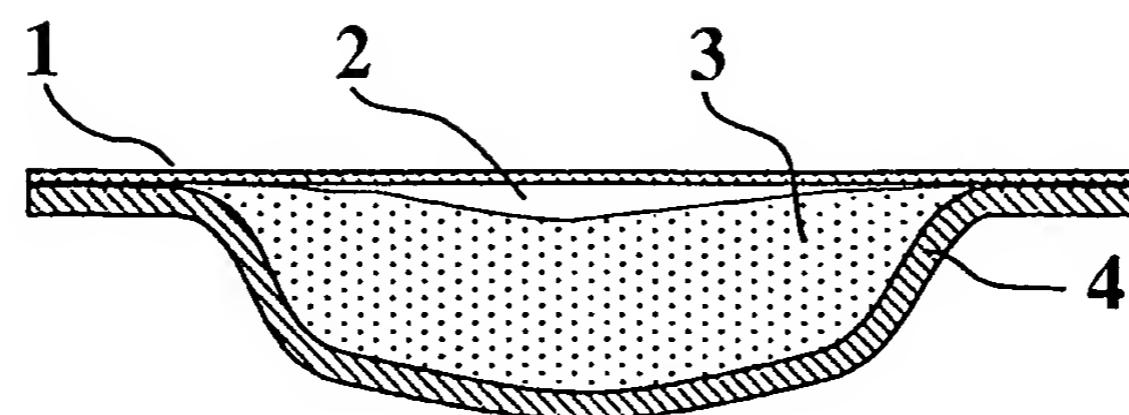


Fig. 3

4/6

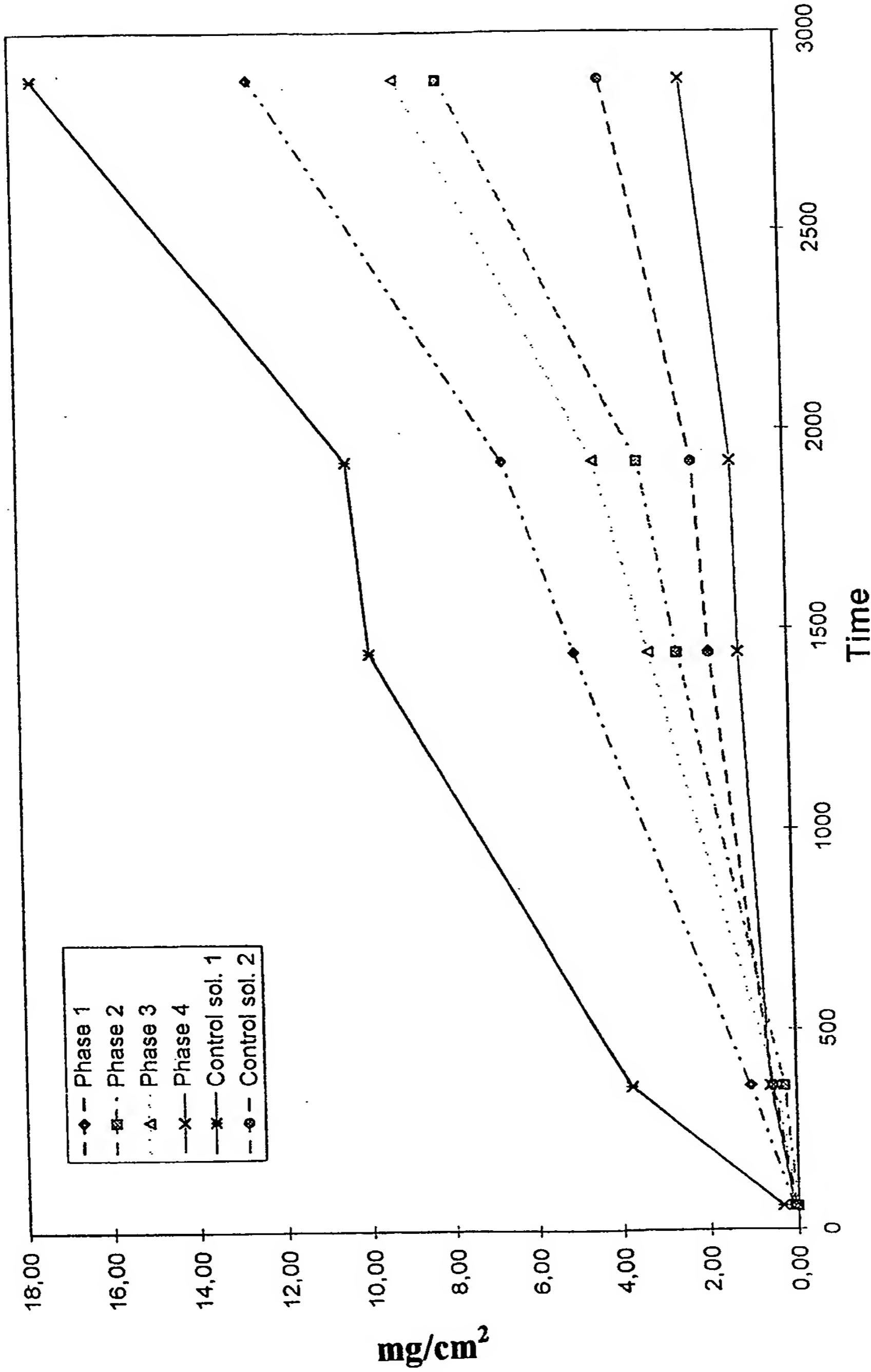


Fig. 4

5/6

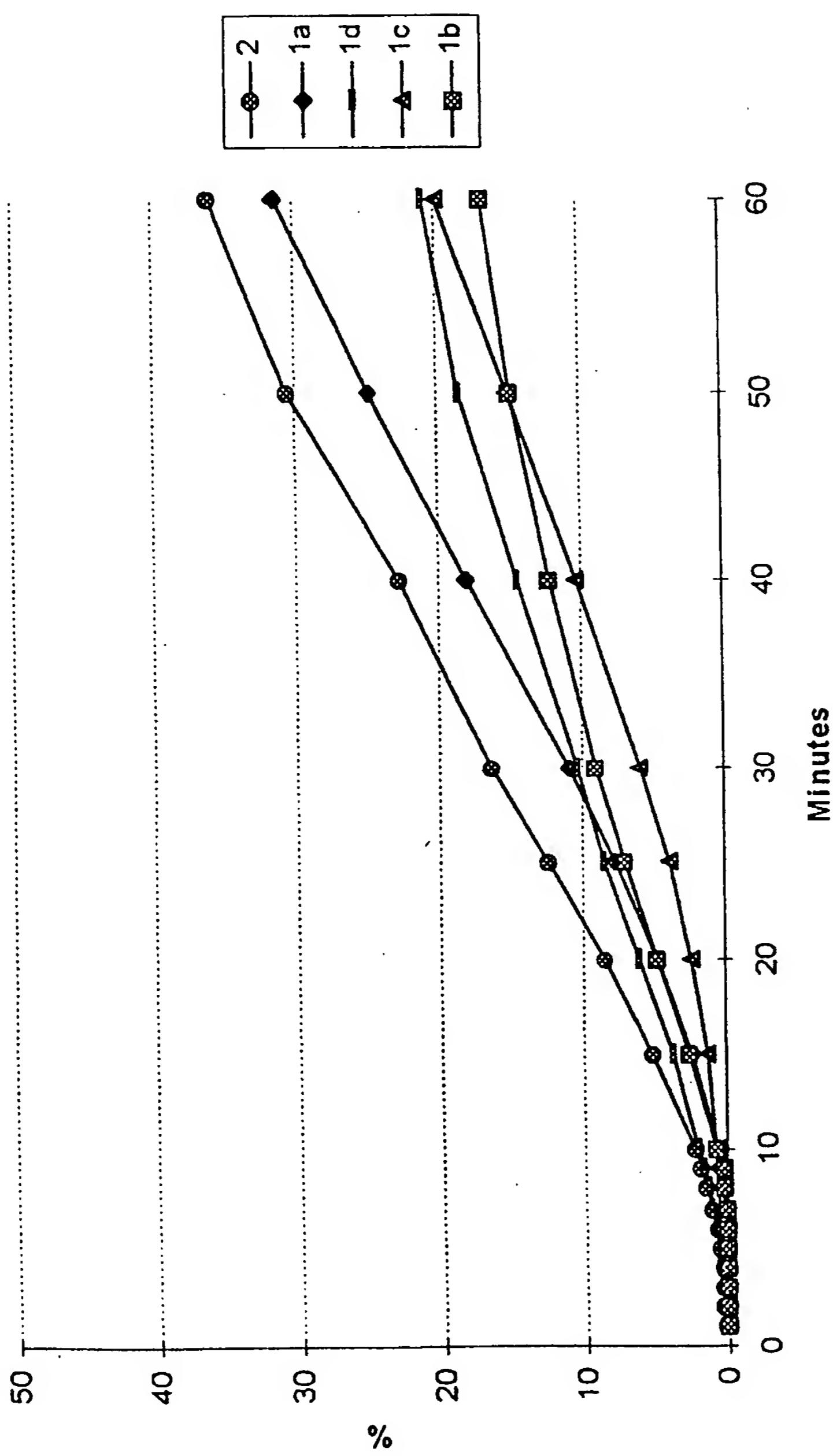
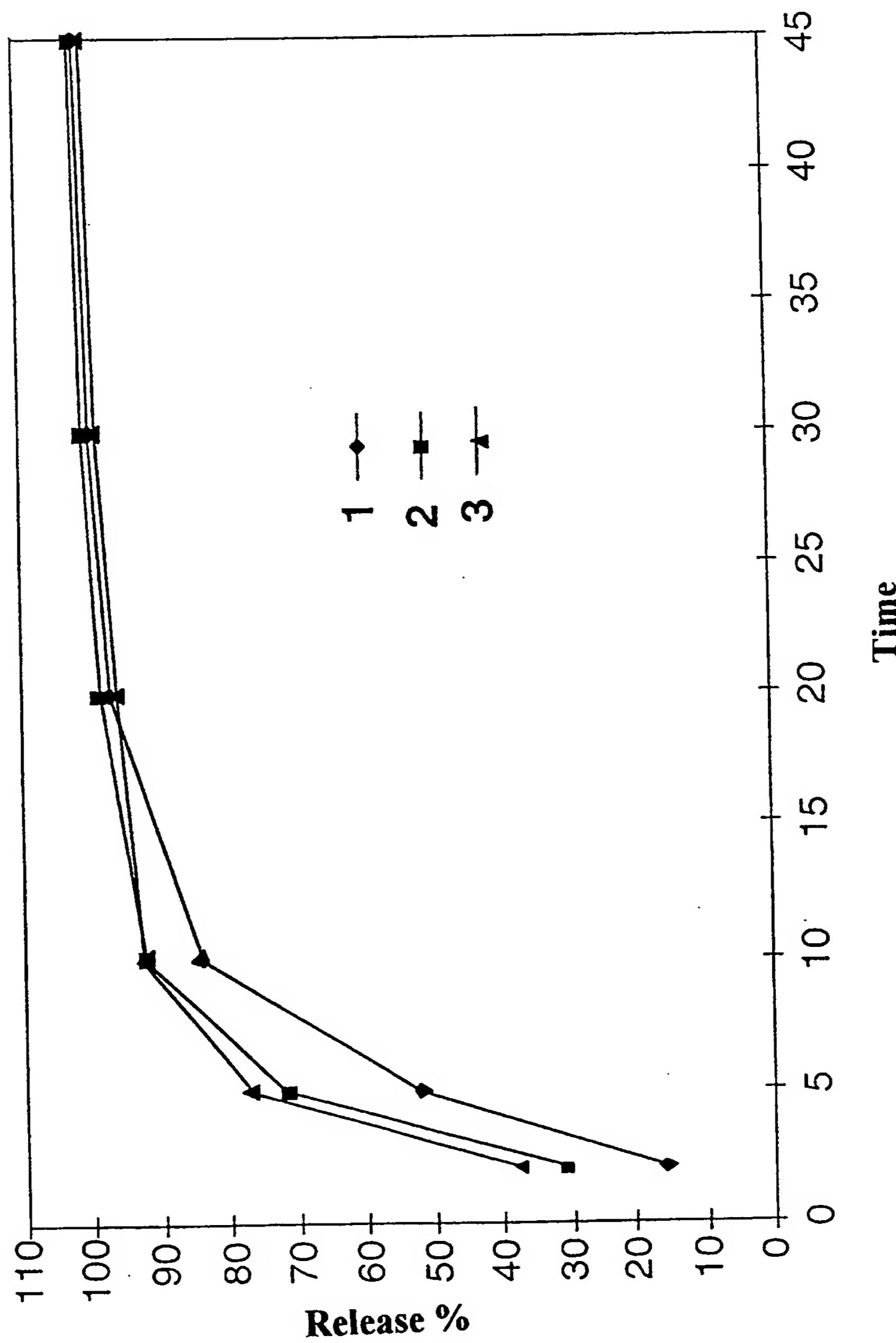


Fig. 5

6/6**Fig. 6**

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 98/01632

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 31/465, A61K 9/00, A61K 9/70
 According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

MEDLINE, EMBASE, WPI, EPODOC

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB 2230439 A (ALEC STANLEY WALTER SHAW), 24 October 1990 (24.10.90) --	1,11-13, 17-23,35-36
X	Dialog Information Services, File 351, Dialog accession no. 010450211, WPI accession no. 95-351528/199546, Khalil A H et al: "Lozenges used to treat smoking habit - comprise mixt. of nicotine resin and substrate, local anaesthetic, bulking agent, minerals, vitamin(s) and sweeteners", AU,B,662877, 19950914 --	1,11-13, 17-23,35-36

 Further documents are listed in the continuation of Box C. See patent family annex.

• Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family
---	--

Date of the actual completion of the international search

22 December 1998

Date of mailing of the international search report

19 -02- 1999

Name and mailing address of the ISA/
Swedish Patent Office
Box 5055, S-102 42 STOCKHOLM
Facsimile No. + 46 8 666 02 86

Authorized officer

Anneli Jönsson
Telephone No. + 46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 98/01632

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E,X	International Journal of Pharmaceuticals, Volume 157, 1997, M.G. Carr et al, "Drug delivery from a liquid crystalline base across Visking and human stratum corneum" page 35 - page 42 --	2-36
X	WO 9713528 A1 (DUMEXALPHARMA A/S), 17 April 1997 (17.04.97), page 4, lines 9-35; page 9, line 1 - page 11, line 8, page 14, lines 19-31; page 17, line 16 --	2-36
A	EP 0289342 A2 (ELAN TRANSDERMAL LIMITED), 2 November 1988 (02.11.88), column 5, lines 37-43, column 8, line 60 - column 9, line 21 --	2-36
A	US 5371109 A (SVEN ENGSTRÖM ET AL), 6 December 1994 (06.12.94) --	2-36
A	US 5531925 A (TOMAS LANDH ET AL), 2 July 1996 (02.07.96), claims --	2-36
A	Dialog Information Service, File 155, Medline, Dialog accession no. 09208524, Medline accession no. 95396883, Wilson AL et al: "Nicotine patches in Alzheimer's disease: pilot study on learning, memory, and safety", Pharmacol Biochem Behav (United States) jun-jul 1995, 51 (2-3) p509-14 --	20
A	Dialog Information Service, File 155, Medline, Dialog accession no. 08126991, Medline accession no. 95167070, Fagerstrom KO et al: "Nicotine may relieve symptoms of Parkinson's disease", Psychopharmacology (Berl) (Germany) Sep 1994, 116 (1) p117-9 --	20

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 98/01632

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>Dialog Information Service, File 155, Medline, Dialog accession no. 09244966, Medline accession no. 97001500, Gusland M. et al: "Pilot trial of nicotine patches as an alternative to corticosteroids in ulcerative colitis", J Gastroenterol (Japan) Aug 1996, 31 (4) p627-9</p> <p>--</p>	20
A	<p>WO 9009808 A1 (SCHERING CORPORATION), 7 Sept 1990 (07.09.90)</p> <p>--</p> <p>-----</p>	21-23

INTERNATIONAL SEARCH REPORT

Int'l. application No.

PCT/SE98/01632

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: 35-36
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Claims 35-36 are directed to methods of treatment of the human or animal body by therapy methods practised on the human or animal body/Rule 39.1(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compositions.
2. Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Group I: claims 1, 11-13(partly), 17-23(partly), 35-36(partly).

Composition comprising nicotine and a local analgesic, or a mixture of local analgesics, for reducing local nicotine-related irritation.

Group II: claims 2-10, 11-13(partly), 14-16, 17-23(partly), 24-33, 35-36 (partly).

Composition for reducing adverse affects of nicotine comprising nicotine, one or more polar lipids and one or more anionic surfactants in amounts to form a liquid crystalline phase or a precursor or offspring thereof when placed in a polar solvent.

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

02/02/99

International application No.

PCT/SE 98/01632

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB 2230439 A	24/10/90	NONE	
WO 9713528 A1	17/04/97	AU 7279296 A CA 2231273 A EP 0871489 A FI 980822 A NO 981633 A	30/04/97 17/04/97 21/10/98 09/04/98 04/06/98
EP 0289342 A2	02/11/88	SE 0289342 T3 AT 161721 T AU 607214 B AU 1534988 A CA 1333051 A DE 3856096 D,T DK 235088 A ES 2112241 T GR 3026563 T JP 1006216 A NO 179963 B,C PT 87377 B US 4946853 A US 5298257 A IE 57786 B	15/01/98 28/02/91 03/11/88 15/11/94 09/07/98 10/01/89 01/04/98 31/07/98 10/01/89 14/10/96 31/08/92 07/08/90 29/03/94 07/04/93
US 5371109 A	06/12/94	CA 1296631 A DE 3778024 A DK 105888 A EP 0314689 A,B SE 0314689 T3 FI 97687 B,C FI 886055 A JP 1503140 T JP 7059523 B NO 175454 B,C SE 457693 B,C SE 8602931 A WO 8800059 A	03/03/92 07/05/92 29/02/88 10/05/89 31/10/96 30/12/88 26/10/89 28/06/95 11/07/94 23/01/89 02/01/88 14/01/88
US 5531925 A	02/07/96	BR 9206593 A EP 0643620 A FI 941538 A JP 7502197 T NO 941191 A SE 9200692 D WO 9306921 A WO 9317819 A AU 2699892 A CA 2120359 A	28/11/95 22/03/95 31/05/94 09/03/95 01/06/94 00/00/00 15/04/93 16/09/93 03/05/93 15/04/93
WO 9009808 A1	07/09/90	AU 5106890 A CA 2046921 A EP 0384386 A EP 0471668 A JP 4503357 T US 4908213 A	26/09/90 22/08/90 29/08/90 26/02/92 18/06/92 13/03/90